

(19) World Intellectual Property  
Organization  
International Bureau



(43) International Publication Date  
31 December 2003 (31.12.2003)

PCT

(10) International Publication Number  
**WO 2004/000819 A1**

(51) International Patent Classification<sup>7</sup>: **C07D 239/24**,  
251/14, 401/06, 401/12, 403/06, 405/06, A61K 31/506,  
31/53, A61P 11/00, 9/00, 19/10, 25/28, 29/00

(21) International Application Number:  
PCT/SE2003/001078

(22) International Filing Date: 23 June 2003 (23.06.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:  
0201976-8 24 June 2002 (24.06.2002) SE

(71) Applicant (for all designated States except US): **ASTRAZENECA AB** [SE/SE]; S-151 85 Södertälje (SE).

(72) Inventors; and

(75) Inventors/Applicants (for US only): **BAILEY, Andrew** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH (GB). **PAIRAUDEAU, Garry** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH (GB). **PATEL, Anil** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH (GB). **THOM, Stephen** [GB/GB]; AstraZeneca R & D Charnwood, Bakewell Road, Loughborough, Leicestershire LE11 5RH (GB).

(74) Agent: **GLOBAL INTELLECTUAL PROPERTY**; AstraZeneca AB, S-151 85 Södertälje (SE).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU,

CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

#### Declaration under Rule 4.17:

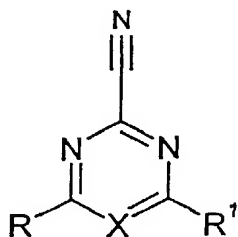
— as to applicant's entitlement to apply for and be granted a patent (Rule 4.17(ii)) for the following designations AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, UZ, VC, VN, YU, ZA, ZM, ZW, ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZM, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG)

#### Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: NEW USE OF PYRIMIDINE - OR TRIAZINE- 2-CARBONITILES FOR TREATING DISEASES ASSOCIATED WITH CYSTEINE PROTEASE ACTIVITY AND NOVEL PYRIMIDINE-2-CARBONITILE DERIVATIVES



(I)

(57) Abstract: The present invention therefore provides use of a compound of formula (I) and compositions for treating diseases associated with cysteine protease activity. The compounds are reversible inhibitors of cysteine proteases S, K, F, L and B. Of particular interest are diseases associated with Cathepsin S. In addition, this invention also discloses processes for the preparation of such inhibitors.

NEW USE OF PYRIMIDINE - OR TRIAZINE- 2-CARBONITILES FOR TREATING DISEASES  
ASSOCIATED  
WITH CYSTEINE PROTEASE ACTIVITY AND NOVEL PYRIMIDINE-2-CARBONITILE DERIVATIVES

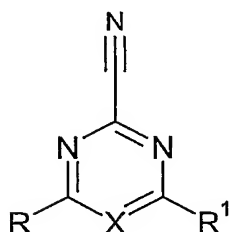
The present invention relates to compounds and compositions for treating diseases associated with cysteine protease activity. The compounds are reversible inhibitors of cysteine proteases S, K, F, L and B. Of particular interest are diseases associated with Cathepsin S. In addition this invention also discloses processes for the preparation of such inhibitors.

BACKGROUND OF THE INVENTION

Cathepsin S is a member of the papain superfamily of cysteine proteases which also encompasses Cathepsins B, H, L, O and K. Cathepsin S plays a key role in the processing of invariant chain in MHC class II complexes allowing the complex to associate with antigenic peptides. MHC class II complexes are then transported to the surface of the cell for presentation to effector cells such as T cells. The process of antigen presentation is a fundamental step in initiation of the immune response. In this respect inhibitors of cathepsin S could be useful agents in the treatment of inflammation and immune disorders such as, but not limited to, asthma, rheumatoid arthritis, multiple sclerosis and Crohn's disease. Cathepsin S has also been implicated in a variety of other diseases involving extracellular proteolysis such as the development of emphysema in COPD through degradation of elastin and in Alzheimers disease.

Other Cathepsins notably K and L have been shown to degrade bone collagen and other bone matrix proteins. Inhibitors of these cysteine proteases would be expected to be useful in the treatment of diseases involving bone resorption such as osteoporosis.

The present invention therefore provides use of a compound of formula (I)



(I)

in which:

X is N or CA where A is hydrogen, halogen,  $\text{CHR}^2\text{R}^3$ ,  $\text{OR}^2$ ,  $\text{NR}^2\text{R}^3$ ,  $\text{SR}^2$ ;

$\text{R}^2$  and  $\text{R}^3$  are independently hydrogen,  $\text{C}_{1-6}$  alkyl or  $\text{C}_{3-6}$  cycloalkyl both of which can optionally contain one or more O, S or  $\text{NR}^4$  groups where  $\text{R}^4$  is hydrogen or  $\text{C}_{1-6}$  alkyl, and can be optionally substituted by aryl, heteroaryl,  $\text{NR}^5\text{R}^6$  where  $\text{R}^5$  and  $\text{R}^6$  together with the nitrogen atom to which they are attached form a 4-7 membered ring optionally containing a further O, S,  $\text{NR}^4$ , or  $\text{R}^2$  and  $\text{R}^3$  together with the nitrogen atom to which they are attached form a 4-7 membered ring optionally containing a further O, S,  $\text{NR}^4$  group, or  $\text{R}^2$  and  $\text{R}^3$  are aryl or heteroaryl groups, both aryl and heteroaryl groups being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy,  $\text{CONR}^7\text{R}^8$ ,  $\text{SO}_2\text{NR}^7\text{R}^8$ ,  $\text{SO}_2\text{R}^4$ , trifluoromethyl,  $\text{NHSO}_2\text{R}^4$ ,  $\text{NHCOR}^4$ , ethylenedioxy, methylenedioxy,  $\text{C}_{1-6}$  alkyl,  $\text{C}_{1-6}$  alkoxy,  $\text{NR}^7\text{R}^8$  or  $\text{SR}^7$  where  $\text{R}^7$  and  $\text{R}^8$  are independently hydrogen or  $\text{C}_{1-6}$  alkyl;

$\text{R}$  and  $\text{R}^1$  are independently a group  $\text{Y}(\text{CH}_2)_p\text{R}^9$  where  $p$  is 0, 1, 2 or 3 and  $\text{Y}$  is O or  $\text{NR}^{10}$  where  $\text{R}^{10}$  is hydrogen,  $\text{C}_{1-6}$  alkyl or  $\text{C}_{3-6}$  cycloalkyl;

and  $\text{R}^9$  is hydrogen,  $\text{C}_{1-6}$  alkyl which can optionally contain one or more O, S or  $\text{NR}^4$  groups where  $\text{R}^4$  is hydrogen or  $\text{C}_{1-6}$  alkyl, or a 3 to 7-membered saturated ring optionally containing a carbonyl group, one or more O, S or N atoms, or an aryl or heteroaryl group containing one to four heteroatoms selected from O, S or N, the saturated ring, aryl and heteroaryl groups all being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy,  $\text{CONR}^7\text{R}^8$ ,  $\text{SO}_2\text{NR}^7\text{R}^8$ ,  $\text{SO}_2\text{R}^4$ , trifluoromethyl,  $\text{NHSO}_2\text{R}^4$ ,  $\text{NHCOR}^4$ , ethylenedioxy, methylenedioxy,  $\text{C}_{1-6}$  alkyl,  $\text{C}_{1-6}$  alkoxy,  $\text{SR}^5$  or  $\text{NR}^{11}\text{R}^{12}$  where  $\text{R}^{11}$  and  $\text{R}^{12}$  are independently hydrogen,  $\text{C}_{1-6}$  alkyl or together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated ring optionally containing a further O, S or  $\text{NR}^4$  group;

or  $\text{R}/\text{R}^1$  is a group  $\text{NR}^{10}(\text{CHR}^{10})\text{CONR}^2\text{R}^3$  or  $\text{NR}^{10}(\text{CH}_2)_q\text{CONR}^2\text{R}^3$  where  $q$  is 1, 2 or 3;

or  $\text{R}/\text{R}^1$  is a group  $\text{NR}^{13}\text{R}^{14}$  where  $\text{R}^{13}$  and  $\text{R}^{14}$  together with the nitrogen atom to which they are attached form a 4 to 7-membered saturated ring optionally containing a carbonyl group, O, S or N atom and optionally substituted by  $\text{C}_{1-6}$  alkyl, amino, hydroxy,  $\text{CO}_2\text{C}_{1-6}$  alkyl, halogen,  $\text{NR}^5\text{R}^6$ ,  $\text{NR}^7\text{R}^8$ ,  $\text{C}_{1-6}$  alkyl $\text{NR}^{17}\text{R}^{18}$  where  $\text{R}^{17}$  and  $\text{R}^{18}$  are independently hydrogen or  $\text{C}_{1-6}$  alkyl,  $\text{CONR}^{15}\text{R}^{16}$  where  $\text{R}^{15}$  and  $\text{R}^{16}$  are independently hydrogen or  $\text{C}_{1-6}$  alkyl, or optionally substituted by aryl, phenoxy, Cophenyl, or a heteroaryl group, the latter four groups being optionally substituted by halogen, amino, hydroxy, cyano, nitro,

carboxy,  $\text{CONR}^7\text{R}^8$ ,  $\text{SO}_2\text{NR}^7\text{R}^8$ ,  $\text{SO}_2\text{R}^4$ , trifluoromethyl,  $\text{NHSO}_2\text{R}^4$ ,  $\text{NHCOR}^4$ , ethylenedioxy, methylenedioxy,  $\text{C}_{1-6}$  alkyl,  $\text{C}_{1-6}$  alkoxy,  $\text{SR}^5$  or  $\text{NR}^{11}\text{R}^{12}$  where  $\text{R}^{11}$  and  $\text{R}^{12}$  are independently hydrogen,  $\text{C}_{1-6}$  alkyl or together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated ring optionally containing a further O, S or  $\text{NR}^4$  group;

and pharmaceutically acceptable salts or solvates thereof, in the manufacture of a medicament for use in the inhibition of cathepsin S in a mammal such as man.

In the context of the present specification, unless otherwise indicated, an alkyl or alkenyl group or an alkyl or alkenyl moiety in a substituent group may be linear or branched. Aryl groups include phenyl and naphthyl. Heteroaryl groups include 5- or 6- membered, 5,6- or 6,6-fused heterocyclic rings containing one or more heteroatoms selected from N, S, O. Examples include pyridine, pyrimidine, thiazole, oxazole, pyrazole, imidazole, furan, thiophene, quinoline, isoquinoline, benzimidazole, benzofuran, benzothiophene and indole.

Certain compounds of formula (I) are capable of existing in stereoisomeric forms. It will be understood that the invention encompasses all geometric and optical isomers of the compounds of formula (I) and mixtures thereof including racemates. Tautomers and mixtures thereof also form an aspect of the present invention.

Preferably X is  $\text{CH}$ ,  $\text{NHR}^2$ ,  $\text{OR}^2$  where  $\text{R}^2$  is preferably H or  $\text{C}_{1-6}$  alkyl.

Preferably R is a group  $\text{Y}(\text{CH}_2)_p\text{R}^7$  where p is 0 or 1 and Y is  $\text{NR}^8$  where  $\text{R}^8$  is hydrogen and  $\text{R}^7$  is substituted phenyl. Preferably  $\text{R}^7$  is phenyl substituted by halogen, especially chloro. More preferably  $\text{R}^7$  is phenyl substituted by chloro in the 4-position.

Preferably  $\text{R}^1$  is a group  $\text{NR}^{13}\text{R}^{14}$  where  $\text{R}^{13}$  and  $\text{R}^{14}$  together with the nitrogen atom to which they are attached form a morpholine ring, piperidine or piperazine ring optionally substituted, or  $\text{R}^1$  is a group  $\text{NR}^9\text{R}^{10}$  where  $\text{R}^{10}$  is H or  $\text{C}_{1-6}$  alkyl and  $\text{R}^9$  is  $\text{C}_{1-6}$  alkyl which can optionally contain one or more O, S or  $\text{NR}^4$  groups where  $\text{R}^4$  is hydrogen or  $\text{C}_{1-6}$  alkyl.

The most preferred substituents for R and  $\text{R}^1$  are those of the examples exemplified herein.

Preferred compounds of the invention include:

4-[(4-Chlorophenyl)amino]-6-(dimethylamino)-1,3,5-triazine-2-carbonitrile,

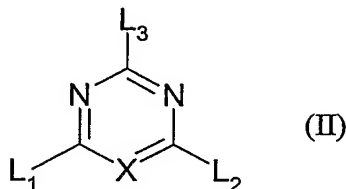
- 4-Morpholin-4-yl-6-(4-phenoxy piperidin-1-yl)-1,3,5-triazine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile,  
4-(7-Azabicyclo[2.2.1]hept-7-yl)-6-[(4-chlorophenyl)amino]-1,3,5-triazine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-pyrrolidin-1-yl-1,3,5-triazine-2-carbonitrile,  
5 4-[(4-Chlorophenyl)amino]-6-piperidin-1-yl-1,3,5-triazine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-(ethylamino)-1,3,5-triazine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-(3-hydroxypyrrolidin-1-yl)-1,3,5-triazine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-[(2-piperidin-1-ylethyl)amino]-1,3,5-triazine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-(4-phenylpiperidin-1-yl)-1,3,5-triazine-2-carbonitrile,  
10 4-[(3-Chlorobenzyl)amino]-6-(dimethylamino)-1,3,5-triazine-2-carbonitrile,  
4-Morpholin-4-yl-6-[(4-morpholin-4-ylphenyl)amino]-1,3,5-triazine-2-carbonitrile,  
4-(2,3-Dihydro-1,4-benzodioxin-6-ylamino)-6-morpholin-4-yl-1,3,5-triazine-2-  
carbonitrile,  
4-Morpholin-4-yl-6-(3-phenylpiperidin-1-yl)-1,3,5-triazine-2-carbonitrile,  
15 4-(1,4'-Bipiperidin-1'-yl)-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile,  
4-[4-(1H-Imidazol-1-yl)piperidin-1-yl]-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile,  
4-[4-(4-Chlorobenzoyl)piperidin-1-yl]-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile,  
4-[4-(5-Chloropyridin-2-yl)piperazin-1-yl]-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile,  
4-Morpholin-4-yl-6-{[3-(2-oxopyrrolidin-1-yl)propyl]amino}-1,3,5-triazine-2-carbonitrile,  
20 1-(4-Cyano-6-morpholin-4-yl-1,3,5-triazin-2-yl)-N,N-diethylpiperidine-3-carboxamide,  
4-[4-(2-Methoxyphenyl)piperazin-1-yl]-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile,  
N~2~-(4-Cyano-6-morpholin-4-yl-1,3,5-triazin-2-yl)-N~1~,N~1~-bis{4-[N-(4-cyano-6-  
morpholin-4-yl-1,3,5-triazin-2-yl)-N-isobutylglycyl]morpholin-3-yl}-N~2~-  
isobutylglycinamide,  
25 4-Morpholin-4-yl-6-[(2-pyridin-3-ylethyl)amino]-1,3,5-triazine-2-carbonitrile,  
4-{[2-(2-Furyl)ethyl]amino}-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-(4-methylpiperazin-1-yl)-1,3,5-triazine-2-carbonitrile,  
4-Azetidin-1-yl-6-[(4-chlorophenyl)amino]-1,3,5-triazine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile,  
30 4-[(4-Methylcyclohexyl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile,  
4-(4-Chlorophenoxy)-6-morpholin-4-ylpyrimidine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-(dimethylamino)pyrimidine-2-carbonitrile,  
4-[(1-Methylpiperidin-4-yl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile,  
4-(Cyclohexylamino)-6-morpholin-4-ylpyrimidine-2-carbonitrile,  
35 4-[(4-Chlorophenyl)amino]-6-pyrrolidin-1-ylpyrimidine-2-carbonitrile,  
4-[(6-Chloropyridin-3-yl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile,

1-{6-[(4-Chlorophenyl)amino]-2-cyanopyrimidin-4-yl}-L-prolinamide,  
 4-(4-Aminopiperidin-1-yl)-6-[(4-chlorophenyl)amino]pyrimidine-2-carbonitrile,  
 4-[(4-Chlorophenyl)amino]-6-(4-pyrrolidin-1-ylpiperidin-1-yl)pyrimidine-2-carbonitrile,  
 4-[(4-Chlorophenyl)amino]-6-[(3-pyrrolidin-1-ylpropyl)amino]pyrimidine-2-carbonitrile,  
 5 tert-Butyl 4-{6-[(4-chlorophenyl)amino]-2-cyanopyrimidin-4-yl}piperazine-1-carboxylate,  
 4-[(4-Chlorophenyl)amino]-6-(cyclopropylamino)pyrimidine-2-carbonitrile,  
 4-[(4-Chlorophenyl)amino]-6-piperazin-1-ylpyrimidine-2-carbonitrile,  
 (2S)-N~2~-{6-[(4-Chlorophenyl)amino]-2-cyanopyrimidin-4-yl}-N~1~,N~1~-bis[4-(N-  
 {6-[(4-chlorophenyl)amino]-2-cyanopyrimidin-4-yl}-L-leucyl)morpholin-3-yl]-L-  
 10 leucinamide,  
 5-Chloro-4-[(4-chlorophenyl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile,  
 4-[(4-Chlorophenyl)amino]-5-methoxy-6-piperazin-1-ylpyrimidine-2-carbonitrile,  
 4-[(4-Chlorophenyl)amino]-5-methoxy-6-morpholin-4-ylpyrimidine-2-carbonitrile,  
 4-[(3S)-3-Aminopyrrolidin-1-yl]-6-[(4-chlorophenyl)amino]-5-methoxypyrimidine-2-  
 15 carbonitrile,  
 4-[(4-Chlorophenyl)amino]-6-{4-[3-(dimethylamino)propyl]piperazin-1-yl}-5-  
 methoxypyrimidine-2-carbonitrile,  
 4-[(4-Chlorophenyl)amino]-6-(dimethylamino)-5-methoxypyrimidine-2-carbonitrile,  
 4-[(4-Chlorophenyl)amino]-5-methoxy-6-(3-oxopiperazin-1-yl)pyrimidine-2-carbonitrile,  
 20 1-{6-[(4-Chlorophenyl)amino]-2-cyano-5-methoxypyrimidin-4-yl}piperidine-3-  
 carboxamide,  
 4-(4-Aminopiperidin-1-yl)-6-[(4-chlorophenyl)amino]-5-methoxypyrimidine-2-  
 carbonitrile,  
 5-Amino-4-[(4-chlorophenyl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile,  
 25 5-Amino-4-[(4-Chlorophenyl)amino]-6-(ethylamino)pyrimidine-2-carbonitrile,  
 and pharmaceutically acceptable salts thereof.

In a further aspect the invention provides a compound of formula (I) as defined above but  
 where X is CH,  $\text{NHR}^2$ ,  $\text{OR}^2$  where  $\text{R}^2$  is preferably H or  $\text{C}_{1-6}$  alkyl. For the novel  
 30 compounds of the invention other preferred groups and compounds are those defined  
 above.

The present invention further provides a process for the preparation of a compound of  
 formula (I) which comprises

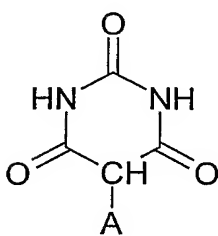
(i) reaction of a compound of general formula (II)



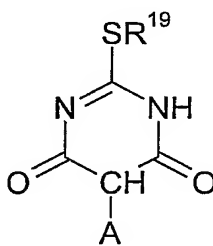
wherein L1, L2 and L3 represent a leaving group (e.g. halide, sulphide, sulfoxide or sulphone group), preferably the sulphide is oxidised to a sulfoxide or sulphone group before displacement. An oxidising agent such as a peracid may be used, for example meta-chloroperoxybenzoic acid in dichloromethane at room temperature.

L1 and L2 may be displaced by R and R<sup>1</sup> respectively where R and R<sup>1</sup> are defined in formula (I) and L3 may be displaced by a cyanide salt. The sequence of displacement of L1, L2 and L3 may be varied.

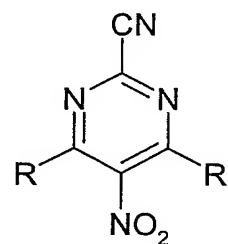
When X=CA and A= OR<sup>2</sup>, SR<sup>2</sup> or CHR<sup>2</sup>R<sup>3</sup> compounds of general formula (II) may be formed by treatment of compounds of general formula (III) and (IV) with phosphorous oxychloride at reflux. R<sup>19</sup> is preferably C<sub>1-6</sub> alkyl or benzyl



(III)



(IV)



(V)

(ii) when X=CA and A=NH<sub>2</sub> reaction of a compound of general formula (V) under a hydrogen atmosphere with palladium catalyst at room temperature.

According to a further feature of the invention there is provided a compound of the formula (I), or a pharmaceutically acceptable salt thereof, for use as a therapeutic agent.

According to a further feature of the present invention there is provided a method for producing inhibition of a cysteine protease in a warm blooded animal, such as man, in need of such treatment, which comprises administering to said animal an effective amount of a compound of the present invention, or a pharmaceutically acceptable salt thereof.

5 The invention also provides a compound of the formula (I), or a pharmaceutically acceptable salt thereof, for use as a medicament; and the use of a compound of the formula (I) of the present invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the inhibition of a cysteine protease in a warm  
10 blooded animal, such as man. In particular the compounds of the invention are useful in the treatment of inflammation and immune disorders such as asthma, rheumatoid arthritis, COPD, multiple sclerosis, Crohn's disease, Alzheimers and pain, such as neuropathic pain. Preferably the compounds of the invention are used to treat pain, in particular neuropathic pain.

15 In particular the invention provides the use of a compound of the formula (I) of the present invention, or a pharmaceutically acceptable salt thereof, in the manufacture of a medicament for use in the inhibition of Cathepsin S in a warm blooded animal, such as man. In order to use a compound of the formula (I) or a pharmaceutically acceptable  
20 salt thereof for the therapeutic treatment of mammals including humans, in particular in the inhibition of a cysteine protease, it is normally formulated in accordance with standard pharmaceutical practice as a pharmaceutical composition.

25 Therefore in another aspect the present invention provides a pharmaceutical composition which comprises a compound of the formula (I) or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable diluent or carrier.

30 The pharmaceutical compositions of this invention may be administered in standard manner for the disease condition that it is desired to treat, for example by oral, rectal or parenteral administration. For these purposes the compounds of this invention may be formulated by means known in the art into the form of, for example, tablets, capsules, aqueous or oily solutions or suspensions, (lipid) emulsions, dispersible powders, suppositories, ointments, creams, drops and sterile injectable aqueous or oily solutions or suspensions.



A suitable pharmaceutical composition of this invention is one suitable for oral administration in unit dosage form, for example a tablet or capsule which contains between 100 mg and 1 g of the compound of this invention.

- 5 In another aspect a pharmaceutical composition of the invention is one suitable for intravenous, subcutaneous or intramuscular injection.

Each patient may receive, for example, an intravenous, subcutaneous or intramuscular dose of 1 mgkg<sup>-1</sup> to 100 mgkg<sup>-1</sup> of the compound, preferably in the range of 5 mgkg<sup>-1</sup> to 20 mgkg<sup>-1</sup> of this invention, the composition being administered 1 to 4 times per day. The intravenous, subcutaneous and intramuscular dose may be given by means of a bolus injection. Alternatively the intravenous dose may be given by continuous infusion over a period of time. Alternatively each patient will receive a daily oral dose which is approximately equivalent to the daily parenteral dose, the composition being administered 1 to 4 times per day.

The following illustrate representative pharmaceutical dosage forms containing the compound of formula (I), or a pharmaceutically-acceptable salt thereof (hereafter compound X), for therapeutic or prophylactic use in humans:

(a)

<u>Tablet I</u>	<u>mg/tablet</u>
Compound X.	100
Lactose Ph.Eur.	179
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

(b)

<u>Tablet II</u>	<u>mg/tablet</u>
Compound X	50
Lactose Ph.Eur.	229
Croscarmellose sodium	12.0
Polyvinylpyrrolidone	6
Magnesium stearate	3.0

5

(c)

<u>Tablet III</u>	<u>mg/tablet</u>
Compound X	1.0
Lactose Ph.Eur.	92
Croscarmellose sodium	4.0
Polyvinylpyrrolidone	2.0
Magnesium stearate	1.0

(d)

<u>Capsule</u>	<u>mg/capsule</u>
Compound X	10
Lactose Ph.Eur.	389
Croscarmellose sodium	100
Magnesium stearate	1.

(e)

<u>Injection I</u>	<u>(50 mg/ml)</u>
Compound X	5.0% w/v
Isotonic aqueous solution	to 100%

Buffers, pharmaceutically-acceptable cosolvents such as polyethylene glycol, polypropylene glycol, glycerol or ethanol or complexing agents such as hydroxy-propyl  $\beta$  cyclodextrin may be used to aid formulation.

5 Note

The above formulations may be obtained by conventional procedures well known in the pharmaceutical art. The tablets (a)-(c) may be enteric coated by conventional means, for example to provide a coating of cellulose acetate phthalate.

10 The following examples illustrate the invention.

**Example 1****4-[(4-Chlorophenyl)amino]-6-(dimethylamino)-1,3,5-triazine-2-carbonitrile****(i) 4,6-Dichloro-N-(4-chlorophenyl)-1,3,5-triazin-2-amine**

4-Chloroaniline (8.28g) was added to a mixture of trichlorotriazine (6g) in acetone/ice-water (1:1, 60ml) and stirred for 1h. The solid was filtered off and dried to give a light brown solid, 8.5g.

MS: APCI(+ve) 275/7(M+1)

**(ii) 6-Chloro-N-(4-chlorophenyl)-N,N-dimethyl-1,3,5-triazine-2,4-diamine**

A solution of dimethylamine in tetrahydrofuran (2M, 1.1ml) was added to a mixture of the product from step (i) (0.3g) in acetone (10ml) and ice-water (10ml). After stirring for 1h, the solid was filtered, washed with water and dried. Yield 0.3g solid.

MS: APCI(+ve) 284(M+1)

**(iii) 4-[(4-Chlorophenyl)amino]-6-(dimethylamino)-1,3,5-triazine-2-carbonitrile**

Sodium cyanide (0.138g) was added to a solution of the product from step (ii) (0.4g) in N,N-dimethylformamide (20ml) and heated at 90°C for 16h. The mixture was partitioned between ethyl acetate and water, a solid formed which was filtered off and purified by RPHPLC 15-85% acetonitrile in aqueous trifluoroacetic acid. Yield 0.05g

MS: APCI(+ve) 275(M+1)

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 10.30(1H, bs), 7.72-7.37(4H, 2xd), 3.14(6H, s)

**Example 2****4-Morpholin-4-yl-6-(4-phenoxy-piperidin-1-yl)-1,3,5-triazine-2-carbonitrile****(i) 2,4-Dichloro-6-morpholin-4-yl-1,3,5-triazine**

Morpholine was added dropwise to stirred solution of trichlorotriazine (6.7g), N,N-diisopropylethylamine (6.5ml) in dichloromethane (50ml) at -78°C. The solid formed was filtered off, washed with water, dried to give a white solid (6.7g).

MS: APCI(+ve) 235(M+1)

**(ii) 4-Morpholin-4-yl-6-(4-phenoxy piperidin-1-yl)-1,3,5-triazine-2-carbonitrile**

4-Phenoxy piperidine (0.15g) was added to a solution of the product from step (i) (0.2g), N,N-diisopropylethylamine (1.47ml) in tetrahydrofuran and stirred at room temperature for 16h. The solvent was evaporated under reduced pressure and the residue purified by chromatography on silica eluting with ether/isohexane (1:2). Yield 0.3g white solid. The solid was dissolved in N,N-dimethylformamide (20ml), sodium cyanide (0.1g) added and heated at 90°C for 32h. The mixture was partitioned between ethyl acetate and water, the organic layer separated, washed with water, brine, dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by RPHPLC 35-95% acetonitrile in aqueous trifluoroacetic acid. Yield 0.079g

MS: APCI(+ve) 367(+H)

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 7.31-6.91(5H, m), 4.66(1H, m), 4.11-4.04(2H, m), 3.70-3.57(10H, m), 2.00-1.95(2H, m), 1.63-1.60(2H, m)

**Examples 3-26**

Examples 3-26 were prepared according to the methods of example 1 or 2 using the appropriate amines.

**Example 3****4-[(4-Chlorophenyl)amino]-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile**

MS: APCI(-ve) 315(M-1)

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 10.41(1H, bs), 7.66-7.31(4H, 2xd), 3.74-3.64(8H, m)

**Example 4****4-(7-Azabicyclo[2.2.1]hept-7-yl)-6-[(4-chlorophenyl)amino]-1,3,5-triazine-2-carbonitrile**

MS: APCI(-ve) 325(M-1)

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 10.37(1H, bs), 7.70-7.35(4H, 2xd), 4.64-4.61(2H, m), 1.74-1.52(8H, m)

**Example 5****4-[(4-Chlorophenyl)amino]-6-pyrrolidin-1-yl-1,3,5-triazine-2-carbonitrile**

5 MS: APCI(-ve) 299(M-1)

1H NMR: (DMSO-d<sub>6</sub>)  $\delta$  10.29(1H, bs), 7.75-7.36(4H, 2xd), 3.54-3.49(4H, m), 1.96-1.90(4H, m)

**Example 6**

10 **4-[(4-Chlorophenyl)amino]-6-piperidin-1-yl-1,3,5-triazine-2-carbonitrile**

MS: APCI(-ve) 313(M-1)

1H NMR: (DMSO-d<sub>6</sub>)  $\delta$  10.29(1H, bs), 7.66-7.38(4H, 2xd), 3.74-3.73(4H, m), 1.64-1.55(6H, m)

15

**Example 7****4-[(4-Chlorophenyl)amino]-6-(ethylamino)-1,3,5-triazine-2-carbonitrile**

MS: APCI(-ve) 273(M-1)

20 1H NMR: (DMSO-d<sub>6</sub>)  $\delta$  10.31(1H, bs), 8.39-7.34(5H, m), 3.36-3.27(2H, q), 1.10(3H, t)

**Example 8****4-[(4-Chlorophenyl)amino]-6-(3-hydroxypyrrolidin-1-yl)-1,3,5-triazine-2-carbonitrile**

25 MS: APCI(-ve) 315(M-1)

1H NMR: (DMSO-d<sub>6</sub>)  $\delta$  10.31(1H, s), 7.76-7.38 (4H, m), 5.06(1H, m), 4.38(1H, m), 3.66-3.45(4H, m), 2.04-1.95(2H, m)

**Example 9**

30 **4-[(4-Chlorophenyl)amino]-6-[(2-piperidin-1-ylethyl)amino]-1,3,5-triazine-2-carbonitrile**

MS: APCI(+ve) 358(M+1)

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 10.38(1H, s), 8.35-7.34(5H, m), 3.37(2H, m), 2.43-2.34(6H, m), 1.48-1.44(6H, m)

5

### Example 10

**4-[(4-Chlorophenyl)amino]-6-(4-phenylpiperidin-1-yl)-1,3,5-triazine-2-carbonitrile**

MS: APCI(-ve) 389(M-1)

10 <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 10.33(1H, bs), 7.68-7.16(9H, m), 4.72-4.69(2H, d), 3.09-2.85(3H, m), 1.88-1.55(4H, m)

### Example 11

**4-[(3-Chlorobenzyl)amino]-6-(dimethylamino)-1,3,5-triazine-2-carbonitrile**

15

MS: APCI(-ve) 287(M-1)

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 8.59-8.44(1H, t), 7.37-7.22(4H, m), 4.47-4.44(2H, m), 3.07-3.03(6H, m)

20

### Example 12

**4-Morpholin-4-yl-6-[(4-morpholin-4-ylphenyl)amino]-1,3,5-triazine-2-carbonitrile**

MS: APCI(+ve) 368(M+1)

25 <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 10.09(1H, s), 7.57-7.48(2H, d), 6.93-6.84(2H, d), 3.72-3.55(12H, m), 3.07-3.00(4H, m)

### Example 13

**4-(2,3-Dihydro-1,4-benzodioxin-6-ylamino)-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile**

30

MS: APCI(-ve) 339(M-1)

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 10.13(1H, s), 7.21-6.80(3H, m), 4.23-3.64(12H, m)

#### Example 14

##### 5 4-Morpholin-4-yl-6-(3-phenylpiperidin-1-yl)-1,3,5-triazine-2-carbonitrile

MS: APCI(+ve) 351(M+1)

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 7.35-7.22(5H, m), 4.67-2.64(13H, m), 1.93-1.48(4H, m)

#### 10 Example 15

##### 4-(1,4'-Bipiperidin-1'-yl)-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile, trifluoroacetate salt

MS: APCI(+ve) 358(M+1)

15 <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 9.23(1H, bm), 4.75-4.64(2H, m), 3.71-3.36(11H, m), 2.93-2.87(4H, m), 2.08-1.37(10H, m)

#### Example 16

##### 4-[4-(1H-Imidazol-1-yl)piperidin-1-yl]-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile

20

MS: APCI(+ve) 341(M+1)

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 9.11(1H, s), 7.89-7.88(1H, s), 7.69-7.68(1H, s), 4.79-4.62(3H, m), 3.74-3.02(10H, m), 2.17-1.88(4H, m)

#### 25 Example 17

##### 4-[4-(4-Chlorobenzoyl)piperidin-1-yl]-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile

MS: APCI(+ve) 413(M+1)

30 <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 8.04-8.02(2H, d), 7.64-7.60(2H, d), 4.62-4.52(2H, m), 3.80-3.69(5H, m), 3.32-3.08(6H, m), 1.87-1.43(4H, m)



**Example 18****4-[4-(5-Chloropyridin-2-yl)piperazin-1-yl]-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile**

5 MS: APCI(+ve) 387(M+1)

1H NMR: (DMSO-d<sub>6</sub>) δ 8.14-8.13(1H, s), 7.65-7.62(1H, d), 6.91-6.89(1H, d), 3.82-3.57(16H, m)

**Example 19**

10 **4-Morpholin-4-yl-6-[[3-(2-oxopyrrolidin-1-yl)propyl]amino]-1,3,5-triazine-2-carbonitrile**

MS: APCI(+ve) 332(M+1)

1H NMR: (DMSO-d<sub>6</sub>) δ 8.10-8.07(1H, t), 3.70-3.62(8H, m), 3.39-3.17(6H, m), 2.22-1.62(6H, m)

**Example 20****1-(4-Cyano-6-morpholin-4-yl-1,3,5-triazin-2-yl)-N,N-diethylpiperidine-3-carboxamide**

20 MS: APCI(+ve) 374(M+1)

1H NMR: (DMSO-d<sub>6</sub>) δ 4.39(2H, m), 3.78-3.60(4H, m), 3.33-2.63(11H, m), 1.80-1.43(4H, m), 1.16-0.92(6H, m)

**Example 21**

25 **4-[4-(2-Methoxyphenyl)piperazin-1-yl]-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile**

MS: APCI(+ve) 382(M+1)

1H NMR: (DMSO-d<sub>6</sub>) δ 6.99-6.87(4H, m), 3.86-3.63(15H, m), 2.99(4H, m)

**Example 22**

**N~2~(4-Cyano-6-morpholin-4-yl-1,3,5-triazin-2-yl)-N~1~,N~1~-bis{4-[N-(4-cyano-6-morpholin-4-yl-1,3,5-triazin-2-yl)-N-isobutylglycyl]morpholin-3-yl}-N~2~-isobutylglycinamide**

MS: APCI(+ve) 390(M+1)

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 4.39-4.36(2H, d), 3.62-3.31(18H, m), 2.05-1.92(1H, m), 0.87-0.85(6H, d)

**Example 23**

**4-Morpholin-4-yl-6-[(2-pyridin-3-ylethyl)amino]-1,3,5-triazine-2-carbonitrile, trifluoroacetate salt**

MS: APCI(+ve) 312(M+1)

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 8.69-8.64(2H, m), 8.22-8.04(2H, m), 7.78-7.70(1H, m), 3.66-3.53(10H, m), 2.97-2.93(2H, t)

**Example 24**

**4-{[2-(2-Furyl)ethyl]amino}-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile**

MS: APCI(-ve) 299(M+1)

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 8.21(1H, t), 7.51(1H, s), 6.34(1H, s), 6.15(1H, s), 3.64-3.62(8H, m), 3.52-3.46(2H, m), 2.86-2.82(2H, m)

**Example 25**

**4-[(4-Chlorophenyl)amino]-6-(4-methylpiperazin-1-yl)-1,3,5-triazine-2-carbonitrile, trifluoroacetate salt**

MS: APCI(+ve) 330(M+1)

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 10.56(1H, bs), 10.05(1H, brs), 7.66-7.40(4H, m), 3.41-3.35(8H, m), 2.81(3H, s)

**Example 26****4-Azetidin-1-yl-6-[(4-chlorophenyl)amino]-1,3,5-triazine-2-carbonitrile**

MS: APCI(-ve) 285(M-1)

1H NMR: (DMSO-d6)  $\delta$  10.32(1H, s), 7.72-7.32(4H, m), 4.15-4.10(4H, m), 2.38-2.30(2H, q)

**Example 27****4-[(4-Chlorophenyl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile****(i) N-(4-Chlorophenyl)-2,6-difluoropyrimidin-4-amine**

4-Chloroaniline was added to a stirred solution of 2,4,6- trifluoropyrimidine (7.7g), potassium carbonate (7.86g) in ethanol (80ml). The mixture was stirred at room temperature for 16h, diluted with water, extracted with ethyl acetate, dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with isohexane/ethyl acetate (4:1). Yield 8.3g cream solid

1H NMR: (DMSO-d6)  $\delta$  10.47(1H, s), 7.58(2H, d), 7.45(2H, d), 6.35(1H, s)

**(ii) 4-[(4-Chlorophenyl)amino]-6-fluoropyrimidine-2-carbonitrile**

Sodium cyanide (0.046g) was added to a solution of the product from step (i) (0.113g) in dimethylsulphoxide (3ml) and stirred at room temperature for 1.5h. The mixture was partitioned between ethyl acetate and water, the organics washed with water, dried (MgSO<sub>4</sub>), and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with isohexane/ethyl acetate (4:1). Yield 0.036g

1H NMR: (DMSO-d6)  $\delta$  10.56(1H, s), 7.57(2H, d), 7.47(2H, d), 6.65(1H, s)

**(iii) 4-[(4-Chlorophenyl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile**

Morpholine (0.16g) was added to a solution of the product from step (ii) (0.16g) in isopropylalcohol (4ml) and stirred for 2h at room temperature. The mixture was partitioned between ethyl acetate and aqueous sodium hydrogencarbonate solution, the organics separated, dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with isohexane/ethyl acetate (1:1). Yield 0.09g

MS: APCI(+ve) 316(M+1)

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 9.65(1H, s), 7.52(2H, d), 7.38(2H, d), 6.08(1H, s), 3.67(4H, t), 3.48(2H, t)

5    **Examples 28-42**

Examples 28-42 were prepared according to the general method of example 27 using the appropriate amines or phenols

**Example 28**

10    **4-[(4-Methylcyclohexyl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile**

MS: APCI(+ve) 302(M+1)

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 7.21-7.18(1H, d), 5.83(1H, s), 3.89(1H, bs), 3.88(4H, m), 3.41(4H, m), 1.63-1.28(9H, m), 0.89(3H, d)

15

**Example 29**

**4-(4-Chlorophenoxy)-6-morpholin-4-ylpyrimidine-2-carbonitrile**

MS: APCI(-ve) 315(M-1)

20    <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 7.53-7.20(4H, 2xd), 6.63(1H, s), 3.65-3.63(8H, m)

**Example 30**

**4-[(4-Chlorophenyl)amino]-6-(dimethylamino)pyrimidine-2-carbonitrile**

25    MS: APCI(+ve) 274(M+1)

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 9.57(1H, s), 7.55-7.34(4H, 2xd), 5.93(1H, s), 3.02(6H, m)

**Example 31**

30    **4-[(1-Methylpiperidin-4-yl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile, trifluoroacetate salt**

MS: APCI(+ve) 303(M+1)

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 9.36(1H, brs), 7.49-7.47(1H, d), 5.76(1H, s), 3.92(1H, bm), 3.67-3.43(8H, 2xm), 3.34-3.10(4H, m), 2.75(3H, s), 2.07-1.68(4H, m)

5 **Example 32**

**4-(Cyclohexylamino)-6-morpholin-4-ylpyrimidine-2-carbonitrile**

MS: APCI(+ve) 288(M+1)

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 7.23-7.21(1H, d), 5.73(1H, s), 3.62-3.42(9H, m), 1.83-1.07(10H, m)

**Example 33**

**4-[(4-Chlorophenyl)amino]-6-pyrrolidin-1-ylpyrimidine-2-carbonitrile**

15 MS: APCI(+ve) 300(M+1)

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 9.55(1H, s), 7.54-7.35(4H, 2xd), 5.79(1H, s), 3.38(4H, m), 1.93(4H, m)

**Example 34**

20 **4-[(6-Chloropyridin-3-yl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile**

MS: APCI(-ve) 315(M-1)

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 9.83(1H, s), 8.55-8.49(1H, s), 8.06-8.02(1H, d), 7.49-7.46(1H, d), 6.10(1H, s), 3.69-3.66(4H, m), 3.52-3.48(4H, m)

25 **Example 35**

**1-{6-[(4-Chlorophenyl)amino]-2-cyanopyrimidin-4-yl}-L-prolinamide**

MS: APCI(+ve) 343(M+1)

30 <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 9.33(1H, s), 7.57-7.24(4H, 2xd), 7.00(2H, bm), 5.81(1H, s), 4.31-3.38(3H, m), 2.26-1.26(4H, m)

**Example 36**

**4-(4-Aminopiperidin-1-yl)-6-[(4-chlorophenyl)amino]pyrimidine-2-carbonitrile, trifluoroacetate salt**

5

MS: APCI(+ve) 329(M+1)

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 9.66(1H, s), 7.88-7.36(7H, m), 6.15(1H, s), 4.23-4.20(2H, m), 3.17-2.96(3H, m), 1.98-1.38(4H, m)

10 **Example 37**

**4-[(4-Chlorophenyl)amino]-6-(4-pyrrolidin-1-ylpiperidin-1-yl)pyrimidine-2-carbonitrile, acetate salt**

MS: APCI(+ve) 383(M+1)

15 

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 9.57(1H, s), 7.53-7.35(4H, 2xd), 6.09(1H, s), 4.06-2.51(9H, m), 1.92-1.90(5H, m), 1.74-1.34(6H, m)

**Example 38**20 

**4-[(4-Chlorophenyl)amino]-6-[(3-pyrrolidin-1-ylpropyl)amino]pyrimidine-2-carbonitrile, trifluoroacetate salt**

MS: APCI(+ve) 357(M+1)

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 9.52(2H, m), 7.63-7.36(5H, 2xd+m), 5.92(1H, bs), 3.54-2.99(8H, m), 2.00-1.84(6H, m)

25

**Example 39**

**tert-Butyl 4-{6-[(4-chlorophenyl)amino]-2-cyanopyrimidin-4-yl}piperazine-1-carboxylate**

30 

MS: APCI(+ve) 415(M+1)

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 9.66(1H, s), 7.52(2H, d), 7.37(2H, d), 6.07(1H, s), 3.54-3.51(4H, m), 3.44-3.41(4H, m), 1.42(9H, s)

**Example 40****4-[(4-Chlorophenyl)amino]-6-(cyclopropylamino)pyrimidine-2-carbonitrile**

MS: APCI(+ve) 286(M+1)

5 1H NMR: (DMSO-d<sub>6</sub>) δ 9.65(1H, s), 7.80(1H, s), 7.53(2H, d), 7.37(2H, d), 6.08(1H, s), 0.76-0.71(2H, m), 0.50-0.46(2H, m)

**Example 41****4-[(4-Chlorophenyl)amino]-6-piperazin-1-ylpyrimidine-2-carbonitrile**

10

MS: APCI(+ve) 315(M+1)

1H NMR: (DMSO-d<sub>6</sub>) δ 9.62(1H, s), 7.53(2H, d), 7.37(2H, d), 6.07(1H, s), 3.46(4H, t), 2.79(4H, t)

15 **Example 42****(2S)-N~2~-{6-[(4-Chlorophenyl)amino]-2-cyanopyrimidin-4-yl}-N~1~,N~1~-bis[4-(N-{6-[(4-chlorophenyl)amino]-2-cyanopyrimidin-4-yl}-L-leucyl)morpholin-3-yl]-L-leucinamide**20 

MS: APCI(+ve) 429(M+1)

1H NMR: (DMSO-d<sub>6</sub>) δ 9.51(1H, s), 7.82(1H, d), 7.46(2H, d), 7.37(2H, d), 6.09(1H, s), 4.87(1H, s), 3.67-3.47(6H, m), 3.35-3.25(2H, m), 1.66-1.53(2H, m), 1.48-1.39(1H, m), 0.92-0.89(6H, m)

25 **Example 43****5-Chloro-4-[(4-chlorophenyl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile****(i) 4-(5-Chloro-2,6-difluoropyrimidin-4-yl)morpholine**

30 Morpholine (0.774mg) was added to a solution of 5-chloro-2,4,6-trifluoropyrimidine (1.5g), N,N-diisopropylethylamine (1.15g) in 1,4-dioxane (30ml) and stirred at room temperature for 16h. The mixture was partitioned between ethyl acetate and water, the organic layer dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The residue was

purified by chromatography on silica eluting with 8% ethyl acetate in isohexane. Yield 0.88g

**(ii) 5-Chloro-N-(4-chlorophenyl)-2-fluoro-6-morpholin-4-ylpyrimidin-4-amine**

4-Chloroaniline (1.44g) was added to a solution of the product from step (i) (0.88g) and N,N-diisopropylethylamine (0.484g) in 1,4-dioxane (15ml) and isopropylalcohol (15ml) and the mixture heated at 110°C for 6 days. The mixture was partitioned between ethyl acetate and water, the organics dried (MgSO<sub>4</sub>), and evaporated under reduced pressure. The solid was triturated with ethyl acetate, filtered and the filtrate purified by chromatography on silica eluting with 3% ethyl acetate in toluene. Yield 0.28g

MS: APCI(+ve) 343/5(M+1)

**(iii) 5-Chloro-4-[(4-chlorophenyl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile**

Sodium cyanide (0.057g) was added to a solution of the product from step (ii) (0.2g) in dimethylsulphoxide (5ml) and the mixture stirred at room temperature. After 18h, the mixture was partitioned between ethyl acetate and water, the organics separated, washed with water, dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with 5% ethyl acetate in toluene. Yield 0.09g

MS: APCI(-ve) 348(M-1)

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 9.34(1H, s), 7.53(2H, d), 7.42(2H, d), 3.71(4H, t), 3.55(4H, t)

**Example 44**

**4-[(4-Chlorophenyl)amino]-5-methoxy-6-piperazin-1-ylpyrimidine-2-carbonitrile, trifluoroacetate salt**

**(i) 5-Methoxy-2-thioxodihydropyrimidine-4,6(1H,5H)-dione**

Thiourea (24g) and methoxymethyl malonate (34g) was added to a solution of sodium (12g) in methanol and the mixture heated under reflux for 10h. The methanol was evaporated under reduced pressure, water (500ml) added and extracted with ether. The aqueous layer was acidified to pH1 with conc. hydrochloric acid, evaporated to ~200ml and the precipitate filtered and dried. Yield 23g

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 11.31(2H, s), 3.48(3H, s)



**(ii) 2-(Ethylthio)-5-methoxypyrimidine-4,6(1H,5H)-dione**

Ethyl iodide (11.2ml) was added dropwise to a stirred mixture of the product from step (i) (23g) and sodium hydroxide (6g) in water (400ml). After 16h the mixture was filtered, the filtrate acidified to pH1 and the precipitate filtered, washed with water and dried. Yield 17.8g

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 12.25(1H, s), 3.59(3H, s), 3.57(1H, s), 3.06(2H, q), 1.28(3H, t)

**(iii) 4,6-Dichloro-2-(ethylthio)-5-methoxypyrimidine**

A mixture of the product from step (ii) (17.8g) and N,N-diethylaniline (20ml) in phosphorus oxychloride (400ml) was heated at 100°C for 3h. The excess reagent was removed under reduced pressure and the residue poured onto ice and extracted with ether. The ether layer was washed with water, dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with 5% ethyl acetate in isohexane. Yield 12.8g

**(iv) 6-Chloro-N-(4-chlorophenyl)-2-(ethylthio)-5-methoxypyrimidin-4-amine**

A solution of the product from step (iii) (4g) and 4-chloroaniline (5.3g) in ethanol (40ml) was heated under reflux for 16h then the solvent removed under reduced pressure. The residue was partitioned between ethyl acetate and 2M hydrochloric acid, the organics washed with water, dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The residue was purified by chromatography on silica eluting with 10-15% ethyl acetate in isohexane. Yield 4.99 g

MS: APCI(+ve) 330/2(M+1)

**(v) 4-Chloro-6-[(4-chlorophenyl)amino]-5-methoxypyrimidine-2-carbonitrile**

A mixture of the product from step (iv) (4.9g) and 3-chloroperoxybenzoic acid (10g, Aldrich 77% max.) in dichloromethane (150ml) was stirred at room temperature for 3h, washed with aqueous sodium metabisulphite solution, water, aqueous sodium hydrogencarbonate solution, water, dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The solid was dissolved in dimethylsulphoxide (40ml), sodium cyanide (1.1g) added and stirred for 2h at room temperature. The mixture was partitioned between ethyl acetate and water, the organics dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The residue

was purified by chromatography on silica eluting with 30% ethyl acetate in isohexane.

Yield 3.23g

MS: APCI(+ve) 295/7(M+1)

**(vi) 4-[(4-Chlorophenyl)amino]-5-methoxy-6-piperazin-1-ylpyrimidine-2-carbonitrile**

A solution of the product from step (v) (0.25g) and piperazine (0.366g) in tetrahydrofuran (8ml) was heated at 60°C for 6h then the solvent removed under reduced pressure. The residue was purified by RPHPLC 15-75% acetonitrile in aqueous trifluoroacetic acid.

Yield 0.139g

MS: APCI(+ve) 345(M+1)

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 9.29(1H, s), 8.92(2H, s), 7.67(2H, d), 7.40(2H, d), 3.83-3.80(4H, m), 3.69(3H, s), 3.25-3.23(4H, m)

Mpt 230°C

#### Examples 45-51

Examples 45-51 were prepared according to the method of example 44 using the appropriate amines

#### Example 45

**4-[(4-Chlorophenyl)amino]-5-methoxy-6-morpholin-4-ylpyrimidine-2-carbonitrile**

MS: APCI(+ve) 346(M+1)

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 9.20(1H, s), 7.67(2H, d), 7.38(2H, d), 3.73-3.70(4H, m), 3.68(3H, s), 3.63-3.61(4H, m)

Mpt 176°C

#### Example 46

**4-[(3S)-3-Aminopyrrolidin-1-yl]-6-[(4-chlorophenyl)amino]-5-methoxypyrimidine-2-carbonitrile, trifluoroacetate salt**

MS: APCI(+ve) 345/7(M+1)

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 9.12(1H, s), 8.10(3H, s), 7.66(2H, d), 7.38(2H, d), 3.91-3.69(5H, m), 3.65(3H, s), 2.33-2.22(1H, m), 2.08-2.01(1H, m)

Mpt 345-7°C

5    **Example 47**

**4-[(4-Chlorophenyl)amino]-6-{4-[3-(dimethylamino)propyl]piperazin-1-yl}-5-methoxypyrimidine-2-carbonitrile, bis-trifluoroacetate salt**

MS: APCI(+ve) 430/2(M+1)

10    <sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) 90°C δ 8.94(1H, s), 7.64(2H, d), 7.35(2H, d), 3.81(4H, brs), 3.70(3H, s), 3.15-3.09(2H, m), 3.00(4H, brs), 2.86(2H, brs), 2.81(6H, s), 2.03-1.95(2H, m)

Mpt 210-2°C

**Example 48**

15    **4-[(4-Chlorophenyl)amino]-6-(dimethylamino)-5-methoxypyrimidine-2-carbonitrile**

MS: APCI(-ve) 302/4(M-1)

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) 90°C δ 9.08(1H, s), 7.66(2H, d), 7.37(2H, d), 3.62(3H, s), 3.13(6H, s)

20    Mpt 173°C

**Example 49**

**4-[(4-Chlorophenyl)amino]-5-methoxy-6-(3-oxopiperazin-1-yl)pyrimidine-2-carbonitrile**

25

MS: APCI(-ve) 357/9(M-1)

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 9.24(1H, s), 8.10(1H, s), 7.67(2H, d), 7.39(2H, d), 4.17(2H, s), 3.85-3.83(2H, m), 3.66(3H, s), 3.32-3.29(2H, m)

Mpt 244°C

30

**Example 50****1-{6-[(4-Chlorophenyl)amino]-2-cyano-5-methoxypyrimidin-4-yl}piperidine-3-carboxamide**

5 MS: APCI(+ve) 387/9 (M+1)

1H NMR: (DMSO-d<sub>6</sub>) δ 9.16(1H, s), 7.68(2H, d), 7.40-7.35(3H, m), 6.89(1H, s), 4.34-4.25(2H, m), 3.65(3H, s), 3.07-2.92(2H, m), 2.35-2.40(1H, m), 1.90-1.51(4H, m)

**Example 51**

10 **4-(4-Aminopiperidin-1-yl)-6-[(4-chlorophenyl)amino]-5-methoxypyrimidine-2-carbonitrile, trifluoroacetate salt**

MS: APCI(+ve) 359/61 (M+1)

1H NMR: (DMSO-d<sub>6</sub>) δ 9.20(1H, s), 7.93(3H, s), 7.67(2H, d), 7.39(2H, d), 4.36-4.32(2H, m), 3.66(3H, s), 3.08-3.01(2H, m), 2.00-1.97(2H, m), 1.57-1.54(2H, m)

15

**Example 52****5-Amino-4-[(4-chlorophenyl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile**

20 **(i) N-(4-Chlorophenyl)-6-morpholin-4-yl-5-nitro-2-(propylthio)pyrimidin-4-amine**

Morpholine (1.31ml) was added dropwise to a stirred solution of 4,6-dichloro-5-nitro-2-thiopropyl pyrimidine (4g), N,N-diisopropylamine (7ml) in dichloromethane (50ml) at 0°C. After 1h, 4-chloroaniline (1.9g) was added, the mixture stirred at room temperature for 24h, then heated under reflux for 24h. The mixture was partitioned between  
25 dichloromethane and 2M hydrochloric acid, the organics washed with water, dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. Yield 5g

MS: APCI(+ve) 410/2 (M+1)

30 **(ii) 4-[(4-Chlorophenyl)amino]-6-morpholin-4-yl-5-nitropyrimidine-2-carbonitrile**

A mixture of the product from step (i) (5g) and 3-chloroperoxybenzoic acid (12g, Aldrich 77% max.) in dichloromethane (200ml) was stirred at room temperature for 2h, washed with aqueous sodium metabisulphite solution, water, aqueous sodium hydrogencarbonate solution, water, dried (MgSO<sub>4</sub>) and evaporated under reduced pressure. The solid was

dissolved in dimethylsulphoxide (30ml), sodium cyanide (2g) added and stirred for 1h at room temperature. Water (500ml) was added and the solid filtered, washed with water, dried and the residue triturated with ether. Yield 1.7g

5 MS: APCI(+ve) 361/3 (M+1)

**(iii) 5-Amino-4-[(4-chlorophenyl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile**

The product from step (ii) (1.7g) and 10% palladium on charcoal (0.2g) in ethyl acetate (300ml) was hydrogenated at 2Bar for 8h, filtered through celite and the solvent  
10 evaporated under reduced pressure. Yield 1.05g

MS: APCI(+ve) 329/331 (M+1)

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 8.66(1H, s), 7.62(2H, d), 7.39(2H, d), 5.53(2H, s), 3.78-3.76(4H, m), 3.08-3.06(4H, m)

15 Mpt 253-4°C

**Example 53**

**5-Amino-4-[(4-Chlorophenyl)amino]-6-(ethylamino)pyrimidine-2-carbonitrile**

Example 53 was prepared according to the general method of example 52 using the  
20 appropriate amine

MS: APCI(+ve) 289/91(M+1)

<sup>1</sup>H NMR: (DMSO-d<sub>6</sub>) δ 8.19(1H, s), 7.50(2H, d), 7.31(2H, d), 6.52(1H, t), 5.20(2H, s), 3.41-3.35(2H, m), 1.18(3H, t)

25 Mpt 211-2°C

**Measurement of Cathepsin S activity.**

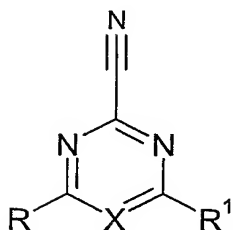
QFRET Technology (Quenched Fluorescent Resonance Energy Transfer) was used to measure the inhibition by test compounds of Cathepsin S-mediated cleavage of the synthetic peptide Z-Val-Val-Arg-AMC. Compounds were screened at five concentrations in duplicate and the pIC<sub>50</sub> values reported.

Synthetic substrate, 20μM [final]Z-Val-Val-Arg-AMC in phosphate buffer were added to a 96 well black Optiplate. The assay plates were pre-read for compound auto fluorescence on SpectraMax Gemini at 355nm excitation and 460nm emission. 250pM [final] rHuman Cathepsin S in phosphate buffer was added and incubated for 2h at room temperature on the SpectraMax Gemini, taking readings every 20min at 355nm excitation and 460nm emission.

Activity Based template (SPTB-8) used the auto fluorescent corrected data to calculate the percentage inhibition for each compound concentration using the relevant plate controls. This data was used to construct inhibition curves and pIC<sub>50</sub> estimated by non-linear regression using a 4 parameter logistic model.

## CLAIMS

1. Use of a compound of formula (I)



(I)

10 in which:

X is N or CA where A is hydrogen, halogen, CHR²R³, OR², NR²R³, SR²;

15 R² and R³ are independently hydrogen, C₁-₆ alkyl or C₃-₆ cycloalkyl both of which can optionally contain one or more O, S or NR⁴ groups where R⁴ is hydrogen or C₁-₆ alkyl, and can be optionally substituted by aryl, heteroaryl, NR⁵R⁶ where R⁵ and R⁶ together with the nitrogen atom to which they are attached form a 4-7 membered ring optionally containing a further O, S, NR⁴, or R2 and R3 together with the nitrogen atom to which they are attached form a 4-7 membered ring optionally containing a further O, S, NR⁴ group, or R2 and R3  
20 are aryl or heteroaryl groups, both aryl and heteroaryl groups being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy, CONR⁷R⁸, SO₂NR⁷R⁸, SO₂R⁴, trifluoromethyl, NHSO₂R⁴, NHCOR⁴, ethylenedioxy, methylenedioxy, C₁-₆ alkyl, C₁-₆ alkoxy, NR⁷R⁸ or SR⁷ where R⁷ and R⁸ are independently hydrogen or C₁-₆ alkyl;

25 R and R¹ are independently a group Y(CH₂)ₚR⁹ where p is 0, 1, 2 or 3 and Y is O or NR¹⁰ where R¹⁰ is hydrogen, C₁-₆ alkyl or C₃-₆ cycloalkyl; and R⁹ is hydrogen, C₁-₆ alkyl which can optionally contain one or more O, S or NR⁴ groups where R⁴ is hydrogen or C₁-₆ alkyl, or a 3 to 7-membered saturated ring optionally containing a carbonyl group, one or more O, S or N atoms, or an aryl or heteroaryl group  
30 containing one to four heteroatoms selected from O, S or N, the saturated ring, aryl and heteroaryl groups all being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy, CONR⁷R⁸, SO₂NR⁷R⁸, SO₂R⁴, trifluoromethyl, NHSO₂R⁴, NHCOR⁴,

ethylenedioxy, methylenedioxy, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, SR<sup>5</sup> or NR<sup>11</sup>R<sup>12</sup> where R<sup>11</sup> and R<sup>12</sup> are independently hydrogen, C<sub>1-6</sub> alkyl or together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated ring optionally containing a further O, S or NR<sup>4</sup> group;

5 or R/R<sup>1</sup> is a group NR<sup>10</sup>(CHR<sup>10</sup>) CONR<sup>2</sup>R<sup>3</sup> or NR<sup>10</sup>(CH<sub>2</sub>)<sub>q</sub>CONR<sup>2</sup>R<sup>3</sup> where q is 1, 2 or 3; or R/R<sup>1</sup> is a group NR<sup>13</sup>R<sup>14</sup> where R<sup>13</sup> and R<sup>14</sup> together with the nitrogen atom to which

they are attached form a 4 to 7-membered saturated ring optionally containing a carbonyl group, O, S or N atom and optionally substituted by C<sub>1-6</sub> alkyl, amino, hydroxy, CO<sub>2</sub>C<sub>1-6</sub> alkyl, halogen, NR<sup>5</sup>R<sup>6</sup>, NR<sup>7</sup>R<sup>8</sup>, C<sub>1-6</sub> alkylNR<sup>17</sup>R<sup>18</sup> where R<sup>17</sup> and R<sup>18</sup> are independently

10 hydrogen or C<sub>1-6</sub> alkyl, CONR<sup>15</sup>R<sup>16</sup> where R<sup>15</sup> and R<sup>16</sup> are independently hydrogen or C<sub>1-6</sub> alkyl, or optionally substituted by aryl, phenoxy, Cophenyl, or a heteroaryl group, the latter four groups being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy, CONR<sup>7</sup>R<sup>8</sup>, SO<sub>2</sub>NR<sup>7</sup>R<sup>8</sup>, SO<sub>2</sub>R<sup>4</sup>, trifluoromethyl, NHSO<sub>2</sub>R<sup>4</sup>, NHCOR<sup>4</sup>,

15 ethylenedioxy, methylenedioxy, C<sub>1-6</sub> alkyl, C<sub>1-6</sub> alkoxy, SR<sup>5</sup> or NR<sup>11</sup>R<sup>12</sup> where R<sup>11</sup> and R<sup>12</sup> are independently hydrogen, C<sub>1-6</sub> alkyl or together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated ring optionally containing a further O, S or NR<sup>4</sup> group;

20 and pharmaceutically acceptable salts or solvates thereof, in the manufacture of a medicament for use in the inhibition of cathepsin S in a mammal such as man.

2. Use compound according to claim 1 in which X is CH, NHR<sup>2</sup>, OR<sup>2</sup> where R<sup>2</sup> is hydrogen or C<sub>1-6</sub> alkyl.

25 3. Use compound according to claim 1 or 2 in which R is a group Y(CH<sub>2</sub>)<sub>p</sub>R<sup>7</sup> where p is 0 or 1 and Y is NR<sup>8</sup> where R<sup>8</sup> is hydrogen and R<sup>7</sup> is substituted phenyl.

4. Use compound according to any one of claims 1 to 3 in which R<sup>1</sup> is a group NR<sup>13</sup>R<sup>14</sup> where R<sup>13</sup> and R<sup>14</sup> together with the nitrogen atom to which they are attached form a  
30 morpholine ring, piperidine or piperazine ring optionally substituted.

5. Use compound according to any one of claims 1 to 3 in which R<sup>1</sup> is a group NR<sup>9</sup>R<sup>10</sup> where R<sup>10</sup> is H or C<sub>1-6</sub> alkyl and R<sup>9</sup> is C<sub>1-6</sub> alkyl which can optionally contain one or more O, S or NR<sup>4</sup> groups where R<sup>4</sup> is hydrogen or C<sub>1-6</sub> alkyl.

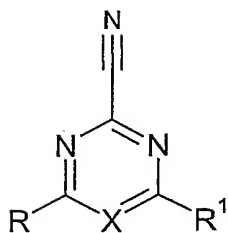
35 6. Use according to claim 1 where the compound of formula (I) is selected from:



- 4-[(4-Chlorophenyl)amino]-6-(dimethylamino)-1,3,5-triazine-2-carbonitrile,  
4-Morpholin-4-yl-6-(4-phenoxy piperidin-1-yl)-1,3,5-triazine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile,  
4-(7-Azabicyclo[2.2.1]hept-7-yl)-6-[(4-chlorophenyl)amino]-1,3,5-triazine-2-carbonitrile,  
5 4-[(4-Chlorophenyl)amino]-6-pyrrolidin-1-yl-1,3,5-triazine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-piperidin-1-yl-1,3,5-triazine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-(ethylamino)-1,3,5-triazine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-(3-hydroxypyrrolidin-1-yl)-1,3,5-triazine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-[(2-piperidin-1-ylethyl)amino]-1,3,5-triazine-2-carbonitrile,  
10 4-[(4-Chlorophenyl)amino]-6-(4-phenylpiperidin-1-yl)-1,3,5-triazine-2-carbonitrile,  
4-[(3-Chlorobenzyl)amino]-6-(dimethylamino)-1,3,5-triazine-2-carbonitrile,  
4-Morpholin-4-yl-6-[(4-morpholin-4-ylphenyl)amino]-1,3,5-triazine-2-carbonitrile,  
4-(2,3-Dihydro-1,4-benzodioxin-6-ylamino)-6-morpholin-4-yl-1,3,5-triazine-2-  
carbonitrile,  
15 4-Morpholin-4-yl-6-(3-phenylpiperidin-1-yl)-1,3,5-triazine-2-carbonitrile,  
4-(1,4'-Bipiperidin-1'-yl)-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile,  
4-[4-(1H-Imidazol-1-yl)piperidin-1-yl]-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile,  
4-[4-(4-Chlorobenzoyl)piperidin-1-yl]-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile,  
4-[4-(5-Chloropyridin-2-yl)piperazin-1-yl]-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile,  
20 4-Morpholin-4-yl-6-[(3-(2-oxopyrrolidin-1-yl)propyl)amino]-1,3,5-triazine-2-carbonitrile,  
1-(4-Cyano-6-morpholin-4-yl-1,3,5-triazin-2-yl)-N,N-diethylpiperidine-3-carboxamide,  
4-[4-(2-Methoxyphenyl)piperazin-1-yl]-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile,  
N~2~-(4-Cyano-6-morpholin-4-yl-1,3,5-triazin-2-yl)-N~1~,N~1~-bis{4-[N-(4-cyano-6-  
morpholin-4-yl-1,3,5-triazin-2-yl)-N-isobutylglycyl]morpholin-3-yl}-N~2~-  
25 isobutylglycinamide,  
4-Morpholin-4-yl-6-[(2-pyridin-3-ylethyl)amino]-1,3,5-triazine-2-carbonitrile,  
4-[[2-(2-Furyl)ethyl]amino]-6-morpholin-4-yl-1,3,5-triazine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-(4-methylpiperazin-1-yl)-1,3,5-triazine-2-carbonitrile,  
4-Azetidin-1-yl-6-[(4-chlorophenyl)amino]-1,3,5-triazine-2-carbonitrile,  
30 4-[(4-Chlorophenyl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile,  
4-[(4-Methylcyclohexyl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile,  
4-(4-Chlorophenoxy)-6-morpholin-4-ylpyrimidine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-(dimethylamino)pyrimidine-2-carbonitrile,  
4-[(1-Methylpiperidin-4-yl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile,  
35 4-(Cyclohexylamino)-6-morpholin-4-ylpyrimidine-2-carbonitrile,  
4-[(4-Chlorophenyl)amino]-6-pyrrolidin-1-ylpyrimidine-2-carbonitrile,

4-[(6-Chloropyridin-3-yl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile,  
 1-{6-[(4-Chlorophenyl)amino]-2-cyanopyrimidin-4-yl}-L-prolinamide,  
 4-(4-Aminopiperidin-1-yl)-6-[(4-chlorophenyl)amino]pyrimidine-2-carbonitrile,  
 4-[(4-Chlorophenyl)amino]-6-(4-pyrrolidin-1-ylpiperidin-1-yl)pyrimidine-2-carbonitrile,  
 5 4-[(4-Chlorophenyl)amino]-6-[(3-pyrrolidin-1-ylpropyl)amino]pyrimidine-2-carbonitrile,  
 tert-Butyl 4-{6-[(4-chlorophenyl)amino]-2-cyanopyrimidin-4-yl}piperazine-1-carboxylate,  
 4-[(4-Chlorophenyl)amino]-6-(cyclopropylamino)pyrimidine-2-carbonitrile,  
 4-[(4-Chlorophenyl)amino]-6-piperazin-1-ylpyrimidine-2-carbonitrile,  
 (2S)-N~2~-{6-[(4-Chlorophenyl)amino]-2-cyanopyrimidin-4-yl}-N~1~,N~1~-bis[4-(N-  
 10 {6-[(4-chlorophenyl)amino]-2-cyanopyrimidin-4-yl}-L-leucyl)morpholin-3-yl]-L-  
 leucinamide,  
 5-Chloro-4-[(4-chlorophenyl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile,  
 4-[(4-Chlorophenyl)amino]-5-methoxy-6-piperazin-1-ylpyrimidine-2-carbonitrile,  
 4-[(4-Chlorophenyl)amino]-5-methoxy-6-morpholin-4-ylpyrimidine-2-carbonitrile,  
 15 4-[(3S)-3-Aminopyrrolidin-1-yl]-6-[(4-chlorophenyl)amino]-5-methoxypyrimidine-2-  
 carbonitrile,  
 4-[(4-Chlorophenyl)amino]-6-{4-[3-(dimethylamino)propyl]piperazin-1-yl}-5-  
 methoxypyrimidine-2-carbonitrile,  
 4-[(4-Chlorophenyl)amino]-6-(dimethylamino)-5-methoxypyrimidine-2-carbonitrile,  
 20 4-[(4-Chlorophenyl)amino]-5-methoxy-6-(3-oxopiperazin-1-yl)pyrimidine-2-carbonitrile,  
 1-{6-[(4-Chlorophenyl)amino]-2-cyano-5-methoxypyrimidin-4-yl}piperidine-3-  
 carboxamide,  
 4-(4-Aminopiperidin-1-yl)-6-[(4-chlorophenyl)amino]-5-methoxypyrimidine-2-  
 carbonitrile,  
 25 5-Amino-4-[(4-chlorophenyl)amino]-6-morpholin-4-ylpyrimidine-2-carbonitrile,  
 5-Amino-4-[(4-Chlorophenyl)amino]-6-(ethylamino)pyrimidine-2-carbonitrile,  
 and pharmaceutically acceptable salts thereof.

7. A compound of formula (I):



(I)

in which:

- 5 X is CA where A is hydrogen, halogen,  $\text{CHR}^2\text{R}^3$ ,  $\text{OR}^2$ ,  $\text{NR}^2\text{R}^3$ ,  $\text{SR}^2$ ;

$\text{R}^2$  and  $\text{R}^3$  are independently hydrogen,  $\text{C}_{1-6}$  alkyl or  $\text{C}_{3-6}$  cycloalkyl both of which can optionally contain one or more O, S or  $\text{NR}^4$  groups where  $\text{R}^4$  is hydrogen or  $\text{C}_{1-6}$  alkyl, and  
 10 can be optionally substituted by aryl, heteroaryl,  $\text{NR}^5\text{R}^6$  where  $\text{R}^5$  and  $\text{R}^6$  together with the nitrogen atom to which they are attached form a 4-7 membered ring optionally containing a further O, S,  $\text{NR}^4$ , or  $\text{R}^2$  and  $\text{R}^3$  together with the nitrogen atom to which they are attached form a 4-7 membered ring optionally containing a further O, S,  $\text{NR}^4$  group, or  $\text{R}^2$  and  $\text{R}^3$  are aryl or heteroaryl groups, both aryl and heteroaryl groups being optionally substituted  
 15 by halogen, amino, hydroxy, cyano, nitro, carboxy,  $\text{CONR}^7\text{R}^8$ ,  $\text{SO}_2\text{NR}^7\text{R}^8$ ,  $\text{SO}_2\text{R}^4$ , trifluoromethyl,  $\text{NHSO}_2\text{R}^4$ ,  $\text{NHCOR}^4$ , ethylenedioxy, methylenedioxy,  $\text{C}_{1-6}$  alkyl,  $\text{C}_{1-6}$  alkoxy,  $\text{NR}^7\text{R}^8$  or  $\text{SR}^7$  where  $\text{R}^7$  and  $\text{R}^8$  are independently hydrogen or  $\text{C}_{1-6}$  alkyl;

$\text{R}$  and  $\text{R}^1$  are independently a group  $\text{Y}(\text{CH}_2)_p\text{R}^9$  where  $p$  is 0, 1, 2 or 3 and  $\text{Y}$  is O or  $\text{NR}^{10}$   
 20 where  $\text{R}^{10}$  is hydrogen,  $\text{C}_{1-6}$  alkyl or  $\text{C}_{3-6}$  cycloalkyl;  
 and  $\text{R}^9$  is hydrogen,  $\text{C}_{1-6}$  alkyl which can optionally contain one or more O, S or  $\text{NR}^4$  groups where  $\text{R}^4$  is hydrogen or  $\text{C}_{1-6}$  alkyl, or a 3 to 7-membered saturated ring optionally containing a carbonyl group, one or more O, S or N atoms, or an aryl or heteroaryl group containing one to four heteroatoms selected from O, S or N, the saturated ring, aryl and  
 25 heteroaryl groups all being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy,  $\text{CONR}^7\text{R}^8$ ,  $\text{SO}_2\text{NR}^7\text{R}^8$ ,  $\text{SO}_2\text{R}^4$ , trifluoromethyl,  $\text{NHSO}_2\text{R}^4$ ,  $\text{NHCOR}^4$ , ethylenedioxy, methylenedioxy,  $\text{C}_{1-6}$  alkyl,  $\text{C}_{1-6}$  alkoxy,  $\text{SR}^5$  or  $\text{NR}^{11}\text{R}^{12}$  where  $\text{R}^{11}$  and  $\text{R}^{12}$  are independently hydrogen,  $\text{C}_{1-6}$  alkyl or together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated ring optionally containing a further O, S or  
 30  $\text{NR}^4$  group;  
 or  $\text{R}/\text{R}^1$  is a group  $\text{NR}^{10}(\text{CHR}^{10})\text{CONR}^2\text{R}^3$  or  $\text{NR}^{10}(\text{CH}_2)_q\text{CONR}^2\text{R}^3$  where  $q$  is 1, 2 or 3;  
 or  $\text{R}/\text{R}^1$  is a group  $\text{NR}^{13}\text{R}^{14}$  where  $\text{R}^{13}$  and  $\text{R}^{14}$  together with the nitrogen atom to which they are attached form a 4 to 7-membered saturated ring optionally containing a carbonyl group, O, S or N atom and optionally substituted by  $\text{C}_{1-6}$  alkyl, amino, hydroxy,  $\text{CO}_2\text{C}_{1-6}$   
 35 alkyl, halogen,  $\text{NR}^5\text{R}^6$ ,  $\text{NR}^7\text{R}^8$ ,  $\text{C}_{1-6}$  alkyl $\text{NR}^{17}\text{R}^{18}$  where  $\text{R}^{17}$  and  $\text{R}^{18}$  are independently hydrogen or  $\text{C}_{1-6}$  alkyl,  $\text{CONR}^{15}\text{R}^{16}$  where  $\text{R}^{15}$  and  $\text{R}^{16}$  are independently hydrogen or  $\text{C}_{1-6}$

alkyl, or optionally substituted by aryl, phenoxy, COphenyl, or a heteroaryl group, the latter four groups being optionally substituted by halogen, amino, hydroxy, cyano, nitro, carboxy,  $\text{CONR}^7\text{R}^8$ ,  $\text{SO}_2\text{NR}^7\text{R}^8$ ,  $\text{SO}_2\text{R}^4$ , trifluoromethyl,  $\text{NHSO}_2\text{R}^4$ ,  $\text{NHCOR}^4$ , ethylenedioxy, methylenedioxy,  $\text{C}_{1-6}$  alkyl,  $\text{C}_{1-6}$  alkoxy,  $\text{SR}^5$  or  $\text{NR}^{11}\text{R}^{12}$  where  $\text{R}^{11}$  and  $\text{R}^{12}$  are independently hydrogen,  $\text{C}_{1-6}$  alkyl or together with the nitrogen atom to which they are attached form a 5- or 6-membered saturated ring optionally containing a further O, S or  $\text{NR}^4$  group;

and pharmaceutically acceptable salts or solvates thereof..

8. A compound of formula (I) as defined in claim 7 for use in therapy.

9. A pharmaceutical composition which comprises a compound of the formula (I) as defined in claim 7 or a pharmaceutically acceptable salt thereof and a pharmaceutically acceptable diluent or carrier.

10. A method for producing inhibition of a cysteine protease in a mammal, such as man, in need of such treatment, which comprises administering to said mammal an effective amount of a compound of the present invention as defined in claim 7 or a pharmaceutically acceptable salt thereof.

## INTERNATIONAL SEARCH REPORT

International application No.:

PCT/SE 03/01078

## A. CLASSIFICATION OF SUBJECT MATTER

IPC7: C07D 239/24, C07D 251/14, C07D 401/06, C07D 401/12, C07D 403/06,  
C07D 405/06, A61K 31/506, A61K 31/53, A61P11/00, 9/00, 19/10, 25/28, 29/00,  
According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC7: C07D, A61K, A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

SE,DK,FI,NO classes as above

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,A	WO 03020278 A1 (NOVARTIS AGET AL), 13 March 2003 (13.03.03)	1-10
	--	
A	WO 0232879 A1 (NAEJA PHARMACEUTICAL INC.), 25 April 2002 (25.04.02)	1-10
	--	
A	WO 9709315 A1 (SIGNAL PHARMACEUTICALS, INC.), 13 March 1997 (13.03.97)	1-10
	--	
A	WO 0055125 A2 (AXYS PHARMACEUTICALS, INC.), 21 Sept 2000 (21.09.00)	1-10
	-- -----	

☐ Further documents are listed in the continuation of Box C. ☒ See patent family annex.

\* Special categories of cited documents:

"A" document defining the general state of the art which is not considered to be of particular relevance  
 "E" earlier application or patent but published on or after the international filing date  
 "L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)  
 "O" document referring to an oral disclosure, use, exhibition or other means  
 "P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance: the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance: the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

"&" document member of the same patent family

Date of the actual completion of the international search

25 Sept 2003

Date of mailing of the international search report

29-09-2003

Name and mailing address of the ISA/  
 Swedish Patent Office  
 Box 5055, S-102 42 STOCKHOLM  
 Facsimile No. +46 8 666 02 86

Authorized officer

Eva Johansson/EÖ  
 Telephone No. +46 8 782 25 00

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/SE03/01078

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This international search report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.: 10  
because they relate to subject matter not required to be searched by this Authority, namely:  
**see next sheet**
2. ☐ Claims Nos.:  
because they relate to parts of the international application that do not comply with the prescribed requirements to such an extent that no meaningful international search can be carried out, specifically:
3. ☐ Claims Nos.:  
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims, it is covered by claims Nos.:

### Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.  
☐ No protest accompanied the payment of additional search fees.

# INTERNATIONAL SEARCH REPORT

Internat application No.  
**PCT/SE03/01078**

Claim 10 relates to methods of treatment of the human or animal body by surgery or by therapy or diagnostic methods practiced on the human or animal body (PCT Rule 39.1(iv)). Nevertheless, a search has been executed for these (this) claim(s). The search has been based on the alleged effects of the compounds or compositions;

## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 03/01078

Patent document cited in search report			Publication date	Patent family member(s)		Publication date
WO	03020278	A1	13/03/03	GB	0121026 D	00/00/00
				GB	0121024 D	00/00/00
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WO	0232879	A1	25/04/02	AU	5057001 A	29/04/02
				CA	2426271 A	25/04/02
				EP	1326848 A	16/07/03
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WO	9709315	A1	13/03/97	AU	726058 B	26/10/00
				AU	726522 B	09/11/00
				AU	7013096 A	27/03/97
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				JP	11512399 T	26/10/99
				US	5935966 A	10/08/99
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				US	5811428 A	22/09/98
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## INTERNATIONAL SEARCH REPORT

International application No.

PCT/SE 03/01078

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO	0055125	A2	21/09/00	AU 3746100 A 04/10/00
				AU 3748600 A 04/10/00
				BG 106003 A 28/06/02
				BG 106013 A 31/05/02
				BR 0009042 A 26/12/01
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				CN 1364155 T 14/08/02
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				EE 200100485 A 17/02/03
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				HR 20010738 A 31/12/02
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				WO 0055126 A 21/09/00